Identification of Small Activating RNAs that Enhance Endogenous OCT4 Expression in Human Mesenchymal Stem Cells.

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Public Summary:
Overexpression of transcription factors has been used to reprogram cell fate. For example, virus-mediated overexpression of four transcription factors OCT4, SOX2, MYC and KLF4, known as Yamanaka factors, can convert somatic cells to induced pluripotent stem (iPS) cells. However, gene-specific switch-on of endogenous gene production without the use of foreign DNA remains a challenge. The small RNA machinery comprised of small RNAs and Argonaute proteins is known to silence gene expression, but can be repurposed to activate gene expression when directed to gene promoters, a phenomenon known as RNA activation or RNAa. By screening of dsRNAs targeting OCT4 promoter, we identified a small activating RNA (saRNA) that activated OCT4 expression in several types of human mesenchymal stem cells (MSCs). We found that saRNA-induced OCT4 activation can be further enhanced by a histone deacetylase inhibitor, valproic acid (VPA). Furthermore, introducing OCT4 saRNA in combination with viruses encoding the remaining three Yamanaka factors (SOX2, MYC and KLF4) into MSCs led to the derivation of partially reprogrammed iPS cells. Findings from this study suggest that, with further optimization, RNAa can be powerful tool to reprogram cell fate by inducing the expression of endogenous genes.

Scientific Abstract:
Ectopic overexpression of transcription factors has been used to reprogram cell fate. For example, virus-mediated overexpression of four transcription factors OCT4, SOX2, MYC and KLF4, known as Yamanaka factors, can convert somatic cells to induced pluripotent stem (iPS) cells. However, gene-specific switch-on of endogenous gene production without the use of foreign DNA remains a challenge. The small RNA machinery comprised of small RNAs and Argonaute proteins is known to silence gene expression, but can be repurposed to activate gene expression when directed to gene promoters, a phenomenon known as RNA activation or RNAa. By screening of dsRNAs targeting OCT4 promoter, we identified a small activating RNA (saRNA) that activated OCT4 expression in several types of human mesenchymal stem cells (MSCs). We found that saRNA-induced OCT4 activation can be further enhanced by a histone deacetylase inhibitor, valproic acid (VPA). Furthermore, introducing OCT4 saRNA in combination with viruses encoding the remaining three Yamanaka factors (SOX2, MYC and KLF4) into MSCs led to the derivation of partially reprogrammed iPS cells. Findings from this study suggest that, with further optimization, RNAa can be powerful tool to reprogram cell fate by inducing the expression of endogenous genes.